Long-term mortality of patients ablated for atrial fibrillation: a population-based epidemiologic study

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Complete List of Authors:	Di Monaco, Antonio; Regional General Hospital "F Miulli", Cardiology Department; University of Foggia, Department of Clinical and Experimental Medicine Vitulano, Nicola; Regional General Hospital "F Miulli", Cardiology Department Troisi, Federica; Regional General Hospital "F Miulli", Cardiology Department Quadrini, Federico; Regional General Hospital "F Miulli", Cardiology Department Guida, Piero; Regional General Hospital "F Miulli", Cardiology Department Grimaldi, Massimo; Regional General Hospital "F Miulli", Cardiology Department

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Long-term mortality of patients ablated for atrial fibrillation: a population-based epidemiologic study

Antonio Di Monaco[1,2] MD, Nicola Vitulano[1] MD, Federica Troisi[1] MD PhD, Federico Quadrini[1] MD, Pietro Guida[1], Massimo Grimaldi[1] MD PhD

1 Cardiology Department, Regional General Hospital “F. Miulli”, Acquaviva delle Fonti, Bari, Italy.
2. Department of Clinical and Experimental Medicine. University of Foggia, Italy

Corresponding author:
Antonio Di Monaco, MD
Cardiology Department, Regional General Hospital “F. Miulli”
Acquaviva delle Fonti, Bari, Italy
E-mail: a.dimonaco@gmail.com
Tel: +390803054111
Fax: +390803054429

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Key words: Cardiac Ablation; Atrial Fibrillation; Mortality, Epidemiology, Cardiovascular disease

Abstract

Objectives. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with substantial morbidity and mortality. Data on long-term risk after catheter ablation of AF are lacking and, moreover, the mortality compared with the general population is not well characterized.

Setting: We analysed data from patients residents in Puglia region underwent to AF ablation between January 2009 and June 2019.

Participants: 1260 patients (914 males, mean age 60±11 years)

Outcome: Vital status and dates of death to December 31, 2019, were obtained by using regional Health Information System. The expected number of deaths was derived using mortality rates from the general regional population by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population.

Results. During follow-up (6449 person-year), 95 deaths were observed (1.47 deaths per 100 person-year). Although overall long-term mortality after AF ablation was not different to that of the general population (SMR 1.05; p=0.658), the number of observed events was significantly increased in patients with heart failure at baseline or developing it during follow-up (SMR 2.40 and 1.75; respectively p<0.001 and p=0.007) and lower in those without (SMR 0.63; p=0.003).

Conclusion. Long-term mortality of patients undergoing AF ablation is similar to that of general population. Patients with heart failure had an increased risk than overall expected while those without seem to have a better risk profile.

Strengths and limitations of this study

- Atrial fibrillation is the most common cardiac arrhythmia that contributes to all-cause mortality and it is a considerable source of morbidity such as stroke and heart failure.
- Data on long-term risk in comparison to general population are lacking, especially after catheter ablation of patients with symptomatic drug-refractory atrial fibrillation.
- After catheter ablation of atrial fibrillation, we found no excess of mortality compared to general population.
- The presence/absence of heart failure stratifies patients at higher/lower risk after the procedure than general population.
- The main purpose of the present epidemiologic study was to analyze overall long term mortality in patients and compare it to general population without identifying prognostic factors

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population [1]. AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health, and health economy. Increasing age is a prominent AF risk factor, but increasing burden of other comorbidities including hypertension, diabetes mellitus, heart failure (HF), coronary artery disease, chronic kidney disease, obesity and obstructive sleep apnoea may contribute to AF development and progression [1]. Atrial fibrillation and HF often co-exist, where one condition promotes the development of the other [2,3]. In both genders, subjects with AF are more likely than subjects without AF to have cardiovascular disease risk factors and preexisting disease, including heart failure [4]. AF may lead to a decrease in ejection fraction and onset of symptomatic HF, particularly if the AF is sustained for long periods or produces high ventricular heart rates. Progressive heart muscle disease is also associated with a higher propensity to develop AF and to progress to more persistent forms of the disease. Optimal treatment of HF in patients with AF has been associated with improved maintenance of sinus rhythm [1].

Mid-term risk of death in AF patients varies according to the clinical setting: from 16.4 deaths per 100 person-year of patients hospitalized in a cardiology ward [5] to a rate of 3.7 fatal events per 100 person-year in AF patients enrolled in anticoagulation trials having mortality among outcomes [6]. In real-world patients with AF, the incidence of death is estimated to be, respectively, 1.0 and 3.6 per 100 person-year in those ablated and non-ablated who receive medical therapy (antiarrhythmic drugs or rate control drugs) [7]. Compared to subjects without AF, in a longitudinal population-based cohort, AF has been detected as a multivariate predictor of death that remained associated with mortality also in subjects initially free of clinically relevant cardiovascular disease [4]. Among death predictors, HF is included in prognostic scores to evaluate mortality risk of AF patients [5,6]. Catheter ablation has become an important treatment modality for patients with symptomatic drug-refractory paroxysmal and non-paroxysmal AF [8]. Furthermore, several randomized clinical trials have reported that both AF and HF outcomes can be improved with catheter ablation [9-12]. In a meta-analysis of randomized clinical trials evaluating patients with AF and coexisting left ventricular systolic dysfunction, catheter ablation has been associated with significant improvements in the clinical, structural, and functional capacity compared with AF medical treatment [13]. Compared to medical therapy, patients ablated for AF have reduced risk of heart failure and stroke as well as the death-rate [7].

Although AF is significantly associated with mortality and morbidity, data on long-term risk after catheter ablation of AF are lacking. Moreover, the mortality compared with the general population is not well characterized and the dynamic of this relative risk is uncertain in terms patient's age and underlying risk profile. There is a paucity of data regarding excess mortality risk in AF patients after cardiac ablation with regard to age and, especially, presence or occurrence of HF. The purpose of this study was to evaluate all-cause mortality and to perform a population-based assessment of the long-term risk of death in patients who underwent to catheter ablation of AF compared to the whole general population.

Methods

Data were derived from the Cardiac Interventional Registry implemented at our hospital. We selected AF ablation procedures performed between January 2009 and June 2019. These patients with drug-refractory AF were treated with catheter ablation according to current guidelines. All patients provided written informed consent. The study complied with the principles of the Declaration of Helsinki. Vital status and dates of death to December 31, 2019, were obtained for residents in Puglia by using regional Health Information System. Follow-up was considered to be administratively censored on December 31, 2019, and was at least 6 months for all patients (maximum, 11 years). Person-years were computed from the date of procedure to death or end of the follow-up. The expected numbers of deaths were derived using mortality rates from the general population of Puglia Region by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics (https://www.istat.it/).

Statistical analysis. Data were reported as mean ± standard deviation, median with interquartile range or percentage. We used the Student's t-test to compare patients' age between groups. Mortality over time was evaluated using Kaplan-Meier curves that were compared with the Log-Rank test. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population. The 95% confidence intervals were estimated using the Poisson distribution. A p value of 0.05 or less was considered statistically significant. All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, Tex).

Patient and Public Involvement: No patient involved

Results

During study period, a total of 1260 patients resident in Puglia Region underwent AF catheter ablation. More than two-thirds were males with a mean age of 60±11 years. Patients aged <55 years were 368 (29.2%) while 453 (36.0%) were in the range 55-65 and 439 (34.8%) were older than 65. Table 1 shows patients' characteristics at the time of procedure. At baseline, 141 (11.2%) patients had history of HF.

Over a total of 6449 person-year follow-up (mean 5.1±3.0 years; median 4.8 and interquartile range 2.6-7.6 years), 95 deaths were observed (1.47 deaths per 100 person-year). Figure 1 (panel A, B and C) shows Kaplan-Meier curves of cumulative mortality over time after catheter ablation of AF in the overall cohort, by age group and in those with or without HF at baseline. Greater age and history of HF were significantly associated to mortality risk (Figure 1, panel B and C). During follow-up, HF was diagnosed in 87 other patients. Table 2 shows detailed outcome data during follow-up. Patients with HF at baseline were significantly older than those without as well as subjects developing HF during follow-up were older than those remaining free from it (both $p<0.001$). The

10-year cumulative mortality rate was 14.2%, 32.2% in the oldest group and 41.5% when HF was pre-existing at the time of procedure. The overall number of deaths observed through follow-up was slightly higher than expected according to regional mortality rate (95 vs 90.8; SMR 1.05 with p=0.658). Age was not related to an excess of mortality than general population (Table 2). Compared to general population risk, patients with HF or developing HF had a significantly higher probability of death while those without HF (at baseline and also during follow-up) experienced a significantly lower number of fatal events than expected. The highest SMR was observed in patients with history of HF at baseline (SMR of 2.40 with $p<0.001$) and in those developing HF during follow-up (SMR of 1.75 with p=0.007) while the lowest was in patients free from HF (SMR of 0.63 with p=0.003). Figure 2 shows the estimated SMR with 95%CI for the overall population and subgroups stratified by patients' age and HF presence at baseline or its occurrence during follow-up.

Discussion

In the current study, we provide a long-term analysis of mortality among patients with symptomatic AF underwent to catheter ablation with respect to age and HF coexistence as well as we assessed the risk of death compared with that in the general regional population over the same period. Beyond the association of the absolute risk with patients' age and presence of HF, the main finding of this study was that the overall long-term mortality of patients ablated for AF was not different than general population. Second, mortality after AF ablation was significantly increased in subjects with a pre-existing history of HF and in those with a diagnosis made during follow-up. In AF patients without HF, observed deaths were lower than expected according to regional mortality rates. The analyses of long-term outcome were based on a cohort from an Italian center with a high procedural volume and on expected risk over a follow-up up to 11 years considering age- and gender-specific annual mortality rates of the general regional population.

Atrial fibrillation increases the risk of mortality and morbidity resulting from stroke, HF, dementia and impaired quality of life [1]. Mortality data in patients undergoing ablation of AF can be extrapolated in studies comparing the ablation procedure and antiarrhythmic therapy. In these studies, the ablation procedure appears to be associated with reduced mortality compared to drug therapy [1,8]. No previous studies reported mortality data in patients undergoing AF ablation compared to the general population. Although age was a great determinant of patients' survival, our analysis showed that the long-term mortality after AF ablation was not higher than the risk of subjects from general population of the same patients' age and gender. These data suggest that after catheter ablation the clinical outcome of patients may be good enough to observe a number of deaths not different than the one expected in general population. However, a mortality gap between patients with and without HF was observed. The coexistence of AF with HF was associated with an excess mortality after the ablation procedure while patients without HF had a mortality rate better than general population.

Although AF leads to increased death rates, a better management of this condition may have reduced the net impact of AF on mortality over time. The overall outcomes and survival rates of patients with AF have significantly improved throughout the last decades. Nevertheless the incidence of hospital-diagnosed AF is increased, the long-term risk of death following onset of AF has decreased remarkably [14]. This effect on mortality might be related with lower temporal risk of heart failure and stroke: the 5-year incidence of HF and ischemic stroke following first-time AF has shown a reduction trend over time [14]. Due to the aging of population, AF remain a major public health concern. However, the prevention of thromboembolic complications has demonstrated efficacy in the reduction of stroke and overall mortality in AF patients [15]. The growing availability and use of catheter ablation of AF may partially explain the mortality reduction. Most of patients are treated with medical therapy that, compared to the ablated one, are older with more frequent comorbidities and at higher risk of death, heart failure admission, and stroke [7]. Evidence of AF beneficial impact on death is lacking. The CABANA trial did not show superiority of ablation versus drug therapy for a combined primary outcome including death, stroke, severe bleeding or cardiac arrest [16] while the CASTLE-AF trial reported lower mortality associated with ablation in patients with AF and heart failure with reduced ejection fraction [10]. In a recent propensity-score-matched analysis including HF patients with preserved ejection fraction and AF, compared to medical therapy, catheter ablation decreases HF hospitalization and symptoms [17]. Although catheter ablation of AF have shown similar effectiveness in patients with HF regardless of presence of systolic dysfunction [18], the significance of results might be related to the limited sample size of studies on catheter ablation of AF that that would be unfeasible to provide sufficient statistical power [19]. Compared to randomized trials, often based on combined end-points to increase statistical power, and epidemiologic evaluations of mortality after catheter ablation of AF, this study was focused on a long-term evaluation of death rate compared to general population over the same period. Findings of our study provide important insight regarding health risks after catheter ablation compared to general population useful in counselling of patients symptomatic for AF.

In many studies, including a randomized controlled trial, catheter ablation for AF consistently improved left ventricular ejection fraction and complication rates, including HF readmissions in HF patients. The recent CASTLE AF trial enrolled patients with AF and HF showing that ablation was superior to medical therapy to improve outcome [10]. Although previous data reported that ablation improves outcome in patients with AF e HF [9-12], our analysis reported that mortality of patients with HF who underwent AF catheter ablation persists higher compared to general population. The mortality data were similar in patients with HF documented at admission compared to patients who had the onset of HF during follow up. These data suggest that an early treatment of AF to avoid persistent forms and an optimal HF treatment are crucial to improve outcome in these patients. The increased mortality found in our cohort of HF patients may be explained by the differences in survival of AF patients with and without HF. The incidence rate after new AF is higher in HF patients with reduced than preserved ejection fraction (30.2 vs 25.7 deaths per 100 person-year) while those without HF are at much more lower risk (12 deaths per 100 person-year) [20]. Moreover, in patients with HF, the association of AF with worse cardiovascular outcomes is significant in patients with reduced and mid-range ejection fraction but not in those with preserved systolic function [21]. Data from Framingham Heart Study show that AF occurs in more than half of individuals with HF and that HF occurs in more than one third of individuals with AF [20]. The onset of AF precedes and follows both HF (both preserved and reduced ejection fraction). However, AF and HF conjointly lead to a poor prognosis, with a higher risk among those with reduced ejection fraction [20]. In absence of HF, according to our data, mortality after cardiac ablation of AF was lower than general population. A significant risk for mortality has been reported for AF at older age (70 years or more) in adjusted analyses based on a large cohort of adult and elderly European men and women [22]. At younger age, from 40 to 69 years, the risk of mortality over a follow-up time of up 10 years was not significantly related to new-onset AF [22]. Patients with HF were older than those without. In general population, other morbidities than cardiovascular diseases affect overall survival. Neoplasms and are the first leading cause of years of life lost and deaths [23]. It is possible that patients underwent to catheter ablation of AF without history of HF and remaining free from it after the procedure are at lower risk than unselected general population also because the risk of AF diagnosis is influenced by socioeconomic factors and patients demographic differences exist in the use of catheter ablation [24-25].

The present study has several limitations. Data are from a single institution that is a reference center for percutaneous ablation of arrhythmias. We compared all causes of death mortality in the study cohort to the general population and we performed subgroup analyses only according to HF presence at baseline or by its occurrence during follow-up. For a complete analysis of the effect of comorbidities on different causes of death, comorbidity information for both patients and reference population are necessary. On the other hand, the main purpose of the present epidemiologic study was to analyze overall long term mortality in patients, selecting those at lower risk, and compare it to general population without identifying prognostic factors.

Conclusions

Long-term mortality of patients undergoing AF ablation is similar to that of the general population suggesting that after this therapeutic procedure there is no excess of mortality than overall expected. Compared to general population risk, patients with HF have a significantly higher probability of death while those without HF seem to have a better risk profile.

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

Not required.

Ethics approval

Ethical approval number 5690 of the Azienda Universitaria Ospedaliera Consorziale - Policlinico Bari of Bari.

Footnotes

All authors contributed to the study conception and design. The first draft of the manuscript was written by Antonio Di Monaco. All authors provided critical feedback on subsequent drafts of the manuscript and have approved the final version.

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Competing interests None declared.

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Figure legends

Figure 1. Kaplan-Meier mortality estimate curve in overall patients (panel A), in those stratified by age at the time of catheter ablation of atrial fibrillation (panel B), and by the presence of comorbidities (panel C).

Figure 2. Standardized mortality ratios relative to the comparison between observed mortality and the expected from general population of Puglia Region based on sex, age and calendar year.

Table 1. Patients' characteristics at the time of catheter ablation of atrial fibrillation.

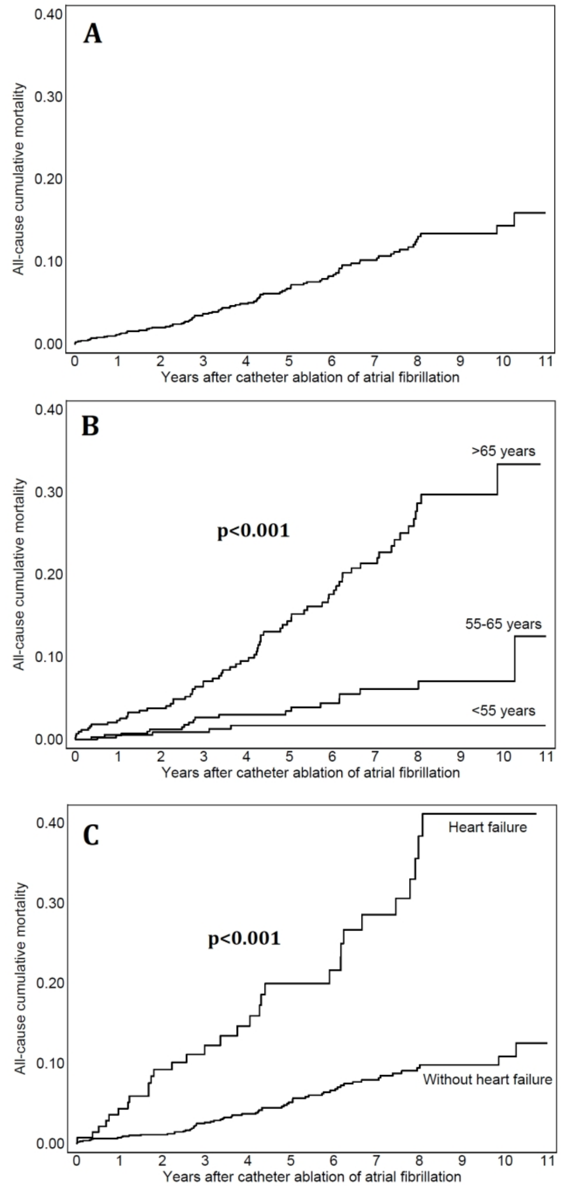
	n=1260
Males	914 (72.5%)
Age (years)	60±11
Hypertension	615 (48.8%)
Diabetes mellitus	115 (9.1%)
Chronic renal disease	48 (3.8%)
Chronic obstructive pulmonary disease	86 (6.8%)
Vascular disease	61 (4.8%)
Previous myocardial infarction	49 (3.9%)
Percutaneous transluminal coronary angioplasty	56 (4.4%)
Coronary artery bypass graft	11 (0.9%)
Cardiac valvular surgery	20 (1.6%)
Heart failure	141 (11.2%)
Stroke or transient ischemic attack	32 (2.5%)
History of cancer	68 (5.4%)

Mean ± Standard Deviation or percentage of patients.

Table 2. Outcome during follow-up.

	Patients n	Age (years)	Deaths (n)	10-Year Mortality Rate (%)	Follow-up (Person-Years)	Event-Rate (100 Person-Years)	Expected Deaths (n)	SMR
Overall	1260	60±11	95	14.2	6449	1.47	90.8	1.05
Age (years)								
<55	368	46±7	5	1.7	1992	0.25	5.2	0.96
55-65	453	60±3	19	7.3	2333	0.81	18.6	1.02
>65	439	72±5	71	32.2	2124	3.34	66.9	1.06
History of heart failure at baseline								
No	1119	59±11	64	10.8	5825	1.10	77.8	0.82
Yes	141	64±11	31	41.5	623	4.98	12.9	2.40
New onset of heart failure during follow-up								
No	1032	59±11	41	7.0	5259	0.80	64.7	0.63
Yes	87	66±12	23	35.1	567	4.06	13.1	1.75

Mean ± Standard Deviation. SMR = Standardized mortality ratio



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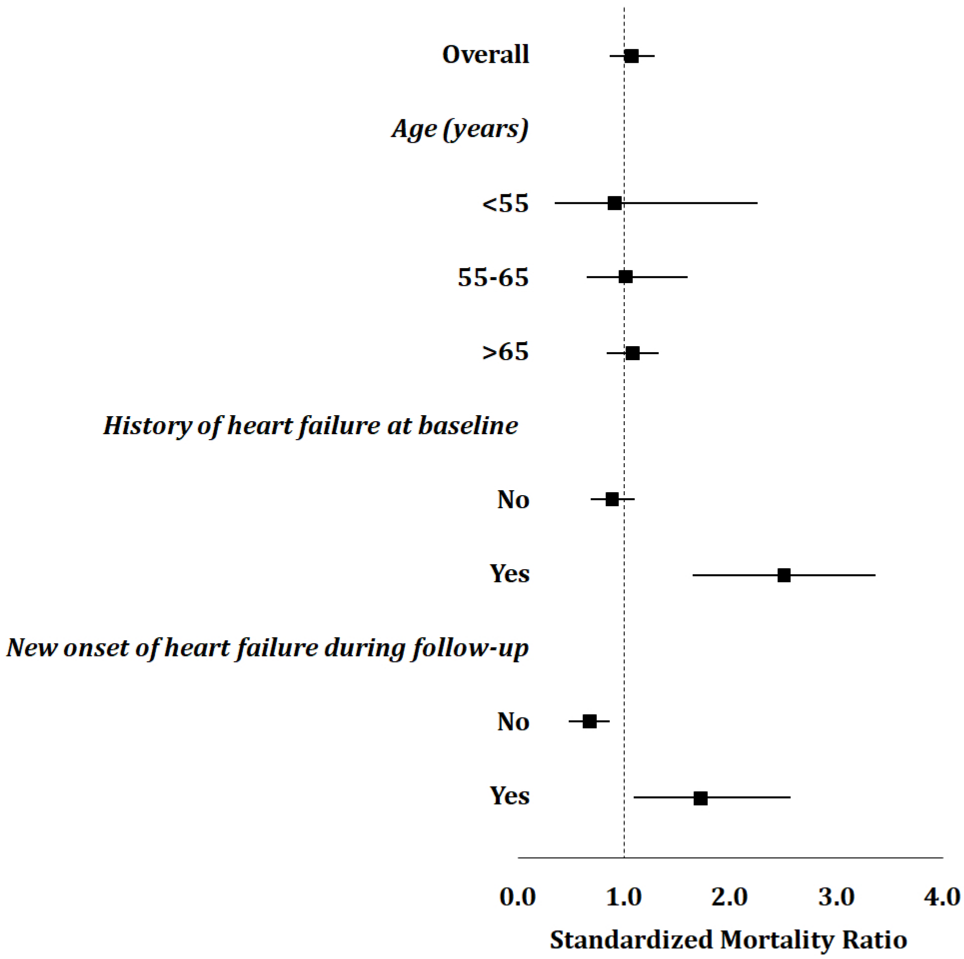

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Long-term mortality of patients ablated for atrial fibrillation: a population-based epidemiological study in Puglia, Italy

Antonio Di Monaco[1,2] MD, Nicola Vitulano[1] MD, Federica Troisi[1] MD PhD, Federico Quadrini[1] MD, Pietro Guida[1], Massimo Grimaldi[1] MD PhD

1 Cardiology Department, Regional General Hospital "F. Miulli", Acquaviva delle Fonti, Bari, Italy.
2. Department of Clinical and Experimental Medicine. University of Foggia, Italy

Corresponding author:
Antonio Di Monaco, MD
Cardiology Department, Regional General Hospital "F. Miulli"
Acquaviva delle Fonti, Bari, Italy
E-mail: a.dimonaco@gmail.com
Tel: +390803054111
Fax: +390803054429

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Conflict of Interest: No conflicts of interest to declare.

Key words: Cardiac Ablation; Atrial Fibrillation; Mortality, Epidemiology, Cardiovascular disease

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Participants: 1260 patients (914 males, mean age 60±11 years)

Outcome: Vital status and dates of death to December 31, 2019, were obtained by using regional Health Information System. The expected number of deaths was derived using mortality rates from the general regional population by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population.

Results. During follow-up (6449 person-year), 95 deaths were observed (1.47 deaths per 100 person-year). Although overall long-term mortality after AF ablation was not different to that of the general population (SMR 1.05; p=0.658), the number of observed events was significantly increased in patients with heart failure at baseline or developing it during follow-up (SMR 2.40 and 1.75; respectively p<0.001 and p=0.007) and lower in those without (SMR 0.63; p=0.003).

Conclusion. Long-term mortality of patients undergoing AF ablation is similar to that of general population. Patients with heart failure had an increased risk than overall expected while those without seem to have a better risk profile.

Strengths and limitations of this study

- Epidemiological study investigating the long-term mortality of patients ablated for atrial fibrillation
- Data were obtained from the Cardiac Interventional Registry implemented at Miulli Hospital regarding procedures performed between January 2009 and June 2019.
- Vital status and dates of death were obtained for residents in Puglia by using regional Health Information System
- Person-years were computed from the date of procedure to death or end of the follow-up
- The expected numbers of deaths were derived using mortality rates from the general population of Puglia Region by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population [1]. AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health, and health economy. Subjects with AF are more likely than subjects without AF to have cardiovascular disease risk factors and preexisting disease, including heart failure [2-4].

Mid-term risk of death in AF patients varies according to the clinical setting: from 16.4 deaths per 100 person-year of patients hospitalized in a cardiology ward [5] to a rate of 3.7 fatal events per 100 person-year in AF patients enrolled in anticoagulation trials having mortality among outcomes [6]. In real-world patients with AF, the incidence of death is estimated to be, respectively, 1.0 and 3.6 per 100 person-year in those ablated and non-ablated who receive medical therapy (antiarrhythmic drugs or rate control drugs) [7]. Compared to subjects without AF, in a longitudinal population-based cohort, AF has been detected as a multivariate predictor of death that remained associated with mortality also in subjects initially free of clinically relevant cardiovascular disease [4]. Among death predictors, HF is included in prognostic scores to evaluate mortality risk of AF patients [5,6]. Catheter ablation has become an important treatment modality for patients with symptomatic drug-refractory paroxysmal and non-paroxysmal AF [8]. Furthermore, several randomized clinical trials have reported that both AF and HF outcomes can be improved with catheter ablation [9-12]. In a meta-analysis of randomized clinical trials evaluating patients with AF and coexisting left ventricular systolic dysfunction, catheter ablation has been associated with significant improvements in the clinical, structural, and functional capacity compared with AF medical treatment [13]. Compared to medical therapy, patients ablated for AF have reduced risk of heart failure and stroke as well as the death-rate [7].

Although AF is significantly associated with mortality and morbidity, data on long-term risk after catheter ablation of AF compared with the general population is not well characterized and the dynamic of this relative risk is uncertain in terms patient's age and underlying risk profile. There is a paucity of data regarding excess mortality risk in AF patients after cardiac ablation with regard to age and, especially, presence or occurrence of HF. The purpose of this study was to evaluate all-cause mortality and to perform a population-based assessment of the long-term risk of death in patients who underwent to catheter ablation of AF compared to the whole general population.

Methods

Data were derived from the Cardiac Interventional Registry implemented at our hospital. Atrial fibrillation and HF were defined according to the European Heart Society guidelines [1,4]. We selected AF ablation procedures performed between January 2009 and June 2019. In particular, all patients had symptomatic drug-refractory AF [1]. All patients provided written informed consent. The study complied with the principles of the Declaration of Helsinki. Vital status and dates of death to December 31, 2019, were obtained for residents in Puglia by using regional Health Information System. Follow-up was considered to be administratively censored on December 31, 2019, and was at least 6 months for all patients (maximum, 11 years). Person-years were computed from the date of procedure to death or end of the follow-up. The expected numbers of deaths were derived using mortality rates from the general population of Puglia Region and Italian general population by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics (https://www.istat.it/).

Statistical analysis. Data were reported as mean ± standard deviation, median with interquartile range or number with percentage. We used the Student's t-test to compare baseline characteristics by presence of HF history. The p values of association between baseline characteristics with time-to-event risk (new HF onset or death during follow-up) were calculated according to Cox proportional-hazards model that was used to estimate Hazard Ratios (HRs) with 95% confidence intervals (CI). Kaplan-Meier curves were used to describe mortality over time and the Log-Rank test to compare survival by age groups or presence of HF history. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population. The 95% CI of SMRs were estimated using the Poisson distribution considering the expected risk of death as exposure variable. A p value of 0.05 or less was considered statistically significant. All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, Tex).

Patient and Public Involvement: No patient involved

Results

During study period, a total of 1260 patients resident in Puglia Region underwent AF catheter ablation. More than two-thirds were males with a mean age of 60±11 years. Patients younger than 55 years were 368 (29.2%) while 453 (36.0%) were in the range 55-65 and 439 (34.8%) were older than 65. At baseline, 141 (11.2%) patients had history of HF. Table 1 shows baseline patients' characteristics by history of HF at the time of procedure of atrial fibrillation ablation. Presence of history of HF was associated to older age and a higher prevalence of hypertension, diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, vascular and coronary artery disease.

Over a total of 6449 person-year follow-up (mean 5.1±3.0 years; median 4.8 and interquartile range 2.6-7.6 years), HF was diagnosed in 87 patients without history of HF at the time of AF ablation procedure and an overall number of 95 deaths were observed. Figure 1 (panel A, B and C) shows Kaplan-Meier curves of cumulative mortality over time after catheter ablation of AF in the overall cohort, by age group and in those with or without HF at baseline. Greater age and history of HF were significantly associated to mortality risk (Figure 1, panel B and C). History of HF had a crude HR of 4.60 (95%CI 3.00-7.08; $p<0.001$) with an age- and sex-adjusted value of 3.06 (1.97-4.76; $p<0.001$).

Table 2 shows baseline patients' characteristics by occurrence during follow-up of new onset of HF or death. Patients with HF during follow-up, compared to those remaining free from HF, were more frequently female, older with a higher prevalence of hypertension, diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, coronary artery disease and more frequently previous cardiac surgery (Table 2). Death during follow-up was associated with an older age and a higher prevalence of hypertension, diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, vascular and coronary artery disease, cancer (Table 2).

Table 3 shows follow-up data and reports mortality in comparison to expected risk in the general population and Figure 2 displays graphically the estimated SMR with 95%CI of observed than expected in regional population. In the overall cohort, the 10-year mortality rate was 14.2% without a significant excess of mortality than expect in the general population of the same age and gender (SMR 1.05; 95%CI 0.86-1.28; p=0.658). Although the 10-year mortality rate increased across age groups (1.7% in <55, 7.3% in 55-65 and 32.3% in those >65years), the comparison with the expected risk was not statistically significant: SMR 0.96 (95%CI 0.40-2.31 p=0.929), 1.02 (95%CI 0.65-1.60 p=0.933) and 1.06 (95%CI 0.84-1.34 p=0.620), respectively for patients in the group of <55, 55-65 and >65years. Patients with HF at baseline or those a new onset during follow-up had a high mortality rate (respectively 41.5% and 35.1%) than those without (Table 3). Compared to general population risk, an excess of mortality was observed in patients with HF at baseline (SMR 2.40; 95%CI 1.69-3.41 p=0.001) and in those with a new onset during follow-up (SMR 1.75; 95%CI 1.17-2.64 p=0.007). In patients without HF, a lower risk than expected was observed especially among those remaining free from HF during follow-up (Table 3). The SMR of 0.82 (95%CI 0.64-1.05; p=0.117) in patients without history of HF at baseline, was significant in those free from HF during follow-up (0.63; 95%CI 0.47-0.86 p=0.003).

When observed mortality was compared to Italian general population, all results were confirmed (Table 3)

Discussion

In the current study, we provide a long-term analysis of mortality among patients with symptomatic AF underwent to catheter ablation with respect to age and HF coexistence as well as we assessed the risk of death compared with that in the general regional population over the same period. Beyond the association of the absolute risk with patients' age and presence of HF, the main finding of this study was that the overall long-term mortality of patients ablated for AF was not different than general population. Second, mortality after AF ablation was higher in subjects with a pre-existing history of HF and in those with a diagnosis made during follow-up. In AF patients without HF, observed deaths were lower than expected according to regional mortality rates. The analyses of long-term outcome were based on a cohort from an Italian center with a high procedural volume and on expected risk over a follow-up up to 11 years considering age- and gender-specific annual mortality rates of the general regional population.

Mortality in patients undergoing ablation of AF appears to be associated with a reduced mortality compared to drug therapy [1,8]. No previous studies reported mortality data in patients undergoing AF ablation compared to the general population. Our analysis showed that the long-term mortality after AF ablation was not higher than the risk of subjects from general population of the same patients' age and gender suggesting that after catheter ablation the clinical outcome of patients may be good enough to observe a number of deaths not different than the one expected in general population. However, a mortality gap between patients with and without HF was observed. The coexistence of AF with HF was associated with an excess mortality after the ablation procedure while patients without HF had a mortality rate better than general population.

Although AF leads to increased death rates, a better management of this condition may have reduced the net impact of AF on mortality over time [14-15]. The growing availability and use of catheter ablation of AF may partially explain the mortality reduction. Most of patients are treated with medical therapy that, compared to the ablated one, are older with more frequent comorbidities and at higher risk of death, heart failure admission, and stroke [7]. Evidence of beneficial impact of AF ablation on death is lacking. The CABANA trial did not show superiority of ablation versus drug therapy for a combined primary outcome including death, stroke, severe bleeding or cardiac arrest [16] while the CASTLE-AF trial reported lower mortality associated with ablation in patients with AF and heart failure with reduced ejection fraction [10]. Recent data including HF patients with preserved ejection fraction and AF, compared to medical therapy, catheter ablation decreases HF hospitalization and symptoms [17-19].

Compared to randomized trials, often based on combined end-points to increase statistical power, and epidemiologic evaluations of mortality after catheter ablation of AF, this study was focused on a long-term evaluation of death rate compared to general population over the same period. Findings of our study provide important insight regarding health risks after catheter ablation compared to general population useful in counselling of patients symptomatic for AF.

Although previous data reported that ablation improves outcome in patients with AF e HF [9-12], our analysis reported that mortality of patients with HF who underwent AF catheter ablation persists higher compared to general population. The mortality data were similar in patients with HF documented at admission compared to patients who had the onset of HF during follow up. These data suggest that an early treatment of AF to avoid persistent forms and an optimal HF treatment are crucial to improve outcome in these patients. The increased mortality found in our cohort of HF patients may be explained by the differences in survival of AF patients with and without HF. The incidence rate after new AF is higher in HF patients with reduced than preserved ejection fraction (30.2 vs 25.7 deaths per 100 person-year) while those without HF are at much more lower risk (12 deaths per 100 person-year) [20]. Moreover, in patients with HF, the association of AF with worse cardiovascular outcomes is significant in patients with reduced and mid-range ejection fraction but not in those with preserved systolic function [21]. Data from Framingham Heart Study show that AF occurs in more than half of individuals with HF and that HF occurs in more than one third of individuals with AF [20]. The onset of AF precedes and follows both HF (both preserved and reduced ejection fraction). However, AF and HF conjointly lead to a poor prognosis, with a higher risk among those with reduced ejection fraction [20]. In absence of HF, according to our data, mortality after cardiac ablation of AF was lower than general population. A significant risk for mortality has been reported for AF at older age (70 years or more) in adjusted analyses based on a large cohort of adult and elderly European men and women [22]. At younger age, from 40 to 69 years, the risk of mortality over a follow-up time of up 10 years was not significantly related to new-onset AF [22]. Patients with HF were older than those without. In general population, other morbidities than cardiovascular diseases affect overall survival. Neoplasms and are the first leading cause of years of life lost and deaths [23]. It is possible that patients underwent to catheter ablation of AF without history of HF and remaining free from it after the procedure are at lower risk than unselected general population also because the risk of AF diagnosis is influenced by socioeconomic factors and patients demographic differences exist in the use of catheter ablation [24-25].

The present study has several limitations. Data are from a single institution that is a reference center for percutaneous ablation of arrhythmias. We compared all causes of death mortality in the study cohort to the general population and we performed subgroup analyses only according to HF presence at baseline or by its occurrence during follow-up. For a complete analysis of the effect of comorbidities on different causes of death, comorbidity information for both patients and reference population are necessary. On the other hand, the main purpose of the present epidemiologic study was to analyze overall long term mortality in patients, selecting those at lower risk, and compare it to general population without identifying prognostic factors.

Conclusions

Long-term mortality of patients undergoing AF ablation is similar to that of the general population suggesting that after this therapeutic procedure there is no excess of mortality than overall expected. Compared to general population risk, patients with HF have a significantly higher probability of death while those without HF seem to have a better risk profile.

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

Not required.

Ethics approval

Ethical approval number 5690 of the Azienda Universitaria Ospedaliera Consorziale - Policlinico Bari of Bari.

Footnotes

Antonio Di Monaco contributed to the study conception and design, wrote the manuscript and have approved the final version,

Nicola Vitulano contributed to the study conception and design, provided critical feedback on subsequent drafts of the manuscript and have approved the final version

Federica Troisi provided critical feedback on subsequent drafts of the manuscript and have approved the final version

Federico Quadrini provided critical feedback on subsequent drafts of the manuscript and have approved the final version

Pietro Guida contributed to the statistical analysis and have approved the final version

Massimo Grimaldi provided critical feedback on subsequent drafts of the manuscript and have approved the final version.

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Competing interests None declared.

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Figure legends

Figure 1. Kaplan-Meier mortality estimate curve in overall patients (panel A), in those stratified by age at the time of catheter ablation of atrial fibrillation (panel B), and by the presence of heart failure (panel C).

Figure 2. Standardized mortality ratios with 95% confidence interval relative to the comparison between observed mortality and the expected from general population of Puglia Region.

Table 1. Baseline patients' characteristics by history of heart failure at the time of procedure of atrial fibrillation ablation.

		Heart failure		
	Overall	**No**	**Yes**	
	n=1260	n=1119	n=141	**p**
Males	914 (72.5%)	804 (71.8%)	110 (78.0%)	0.122
Age (years)	60±11	60±11	64±11	<0.001
Hypertension	615 (48.8%)	530 (47.4%)	85 (60.3%)	0.004
Diabetes mellitus	115 (9.1%)	88 (7.9%)	27 (19.1%)	<0.001
Chronic renal disease	48 (3.8%)	31 (2.8%)	17 (12.1%)	<0.001
COPD	86 (6.8%)	56 (5.0%)	30 (21.3%)	<0.001
Vascular disease	61 (4.8%)	45 (4.0%)	16 (11.3%)	<0.001
Coronary artery disease	86 (6.8%)	65 (5.8%)	21 (14.9%)	<0.001
Cardiac surgery	30 (2.4%)	24 (2.1%)	6 (4.3%)	0.136
Previous stroke or TIA	32 (2.5%)	29 (2.6%)	3 (2.1%)	1.000
History of cancer	68 (5.4%)	58 (5.2%)	10 (7.1%)	0.344

Mean ± Standard Deviation or percentage of patients. COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischemic Attack.

Table 2. Association of baseline patients' characteristics new heart failure onset of heart failure and death during follow-up.

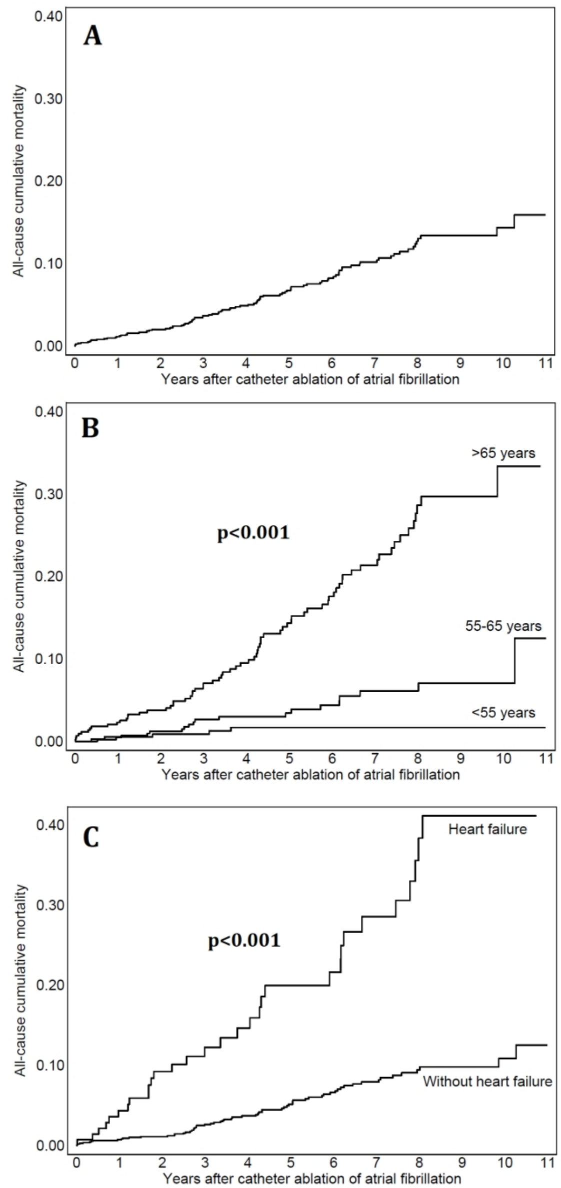
	*New heart failure onset			Death		
	No	Yes		No	Yes	
	n=1032	n=87	p	n=1165	n=95	p
Males	751 (72.8%)	53 (60.9%)	0.038	840 (72.1%)	74 (77.9%)	0.242
Age (years)	59±11	66±12	<0.001	59±11	72±10	<0.001
Hypertension	469 (45.4%)	61 (70.1%)	0.001	552 (47.4%)	63 (66.3%)	<0.001
Diabetes mellitus	64 (6.2%)	24 (27.6%)	<0.001	89 (7.6%)	26 (27.4%)	<0.001
Chronic renal disease	26 (2.5%)	5 (5.7%)	0.044	32 (2.7%)	16 (16.8%)	<0.001
COPD	47 (4.6%)	9 (10.3%)	0.037	58 (5.0%)	28 (29.5%)	<0.001
Vascular disease	41 (4.0%)	4 (4.6%)	0.583	50 (4.3%)	11 (11.6%)	<0.001
Coronary artery disease	54 (5.2%)	11 (12.6%)	0.002	69 (5.9%)	17 (17.9%)	0.003
Cardiac surgery	17 (1.6%)	7 (8.0%)	<0.001	27 (2.3%)	3 (3.2%)	0.591
Previous stroke or TIA	27 (2.6%)	2 (2.3%)	0.804	29 (2.5%)	3 (3.2%)	0.819
History of cancer	52 (5.0%)	6 (6.9%)	0.087	58 (5.0%)	10 (10.5%)	0.005

Mean ± Standard Deviation or percentage of patients. COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischemic Attack. *New heart failure onset refers to 1119 patients without history of heart failure at the time of procedure of atrial fibrillation ablation. The p values were calculated according to Cox proportional-hazards model.

Table 3. Mortality and expected risk during follow-up with standardized mortality ratios in relation to age categories, history of heart failure and development of heart failure.

	Patients n	Deaths (n)	10-year mortality rate (%)	Follow-up (Person-Years)	Event-Rate (100 Person-Years)	Expected Deaths in Puglia (n)	SMR (95%CI) vs Puglia	Expected Deaths in Italy (n)	SMR (95%CI) vs Italy
Overall	1260	95	14.2	6449	1.47	90.8	1.05 (0.86-1.28) p=0.658	92.9	1.02 (0.84-1.25) p=0.829
Age (years)									
<55	368	5	1.7	1992	0.25	5.2	0.96 (0.40-2.31) p=0.929	5.4	0.93 (0.39-2.23) p=0.0.871
55-65	453	19	7.3	2333	0.81	18.6	1.02 (0.65-1.60) p=0.933	19.6	0.97 (0.62-1.52) p=0.888
>65	439	71	32.2	2124	3.34	66.9	1.06 (0.84-1.34) p=0.620	67.9	1.05 (0.83-1.32) p=0.708
History of heart failure at baseline									
No	1119	64	10.8	5825	1.10	77.8	0.82 (0.64-1.05) p=0.117	79.7	0.80 (0.63-1.03) p=0.079
Yes	141	31	41.5	623	4.98	12.9	2.40 (1.69-3.41) p<0.001	13.2	2.34 (1.65-3.33) p<0.001
**New onset of heart failure during follow-up*									
No	1032	41	7.0	5259	0.78	64.7	0.63 (0.47-0.86) p=0.003	66.3	0.62 (0.46-0.84) p=0.002
Yes	87	23	35.1	567	4.06	13.1	1.75 (1.17-2.64) p=0.007	13.4	1.72 (1.14-2.59) p=0.009

CI = Confidence Interval; SMR = Standardized mortality ratio. *New heart failure onset refers to 1119 patients without history of heart failure at the time of procedure of atrial fibrillation ablation. The p values were calculated according to Poisson model.



Kaplan-Meier mortality estimate curve in overall patients (panel A), in those stratified by age at the time of catheter ablation of atrial fibrillation (panel B), and by the presence of heart failure (panel C).

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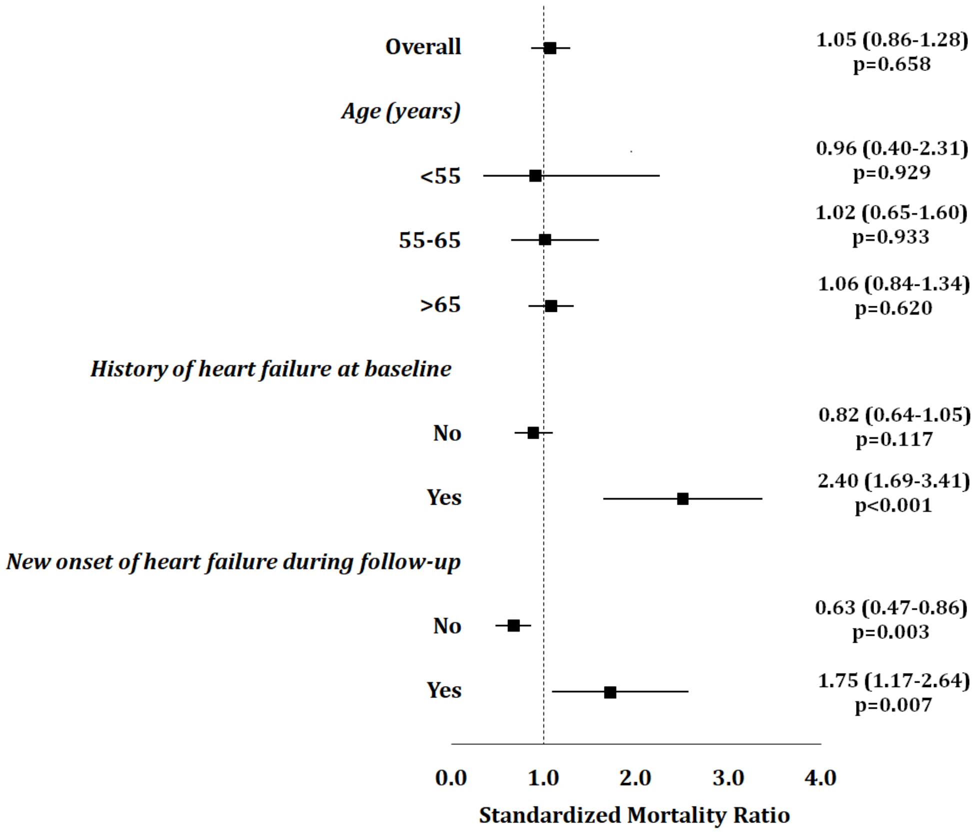

Standardized mortality ratios with 95% confidence interval relative to the comparison between observed mortality and the expected from general population of Puglia Region.

304x261mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 2; rows 1-22)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (page 4, rows 1-23)
Objectives	3	State specific objectives, including any prespecified hypotheses (page 4, rows 24-24) (page 5, rows 1-4)
Methods		
Study design	4	Present key elements of study design early in the paper (page 5, rows 5-12)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 5, rows 13-18)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case (page 5, rows 5-18)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (page 5, rows 19-26) (page 6, rows 1-4)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (page 5, rows 19-26) (page 6, rows 1-4)
Bias	9	Describe any efforts to address potential sources of bias (page 5, rows 19-26) (page 6, rows 1-4) (page 10; rows 9-16)
Study size	10	Explain how the study size was arrived at (page 5, rows 19-26) (page 6, rows 1-4)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (page 5, rows 19-26) (page 6, rows 1-4)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of

sampling strategy (page 5, rows 19-26) (page 6, rows 1-4)

(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram (page 6, rows 8-9)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (page 6, rows 8-15)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures (page 6, rows 16-20) (page 7, rows 1-22)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (page 6, rows 16-20) (page 7, rows 1-22)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (page 6, rows 16-20) (page 7, rows 1-22)
Discussion		
Key results	18	Summarise key results with reference to study objectives (page 7, rows 25-26) (page 8, rows 1-9)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 10, rows 9-16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (page 10, rows 18-22)
Generalisability	21	Discuss the generalisability (external validity) of the study results (page 9, rows 4-11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page 11, row 21)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Long-term mortality of patients ablated for atrial fibrillation: a population-based epidemiological study in Apulia, Italy

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Long-term mortality of patients ablated for atrial fibrillation: a population-based epidemiological study in Apulia, Italy

Antonio Di Monaco[1,2] MD, Nicola Vitulano[1] MD, Federica Troisi[1] MD PhD, Federico Quadrini[1] MD, Pietro Guida[1], Massimo Grimaldi[1] MD PhD

1 Cardiology Department, Regional General Hospital "F. Miulli", Acquaviva delle Fonti, Bari, Italy.
2 Department of Clinical and Experimental Medicine, University of Foggia, Italy.

Corresponding author:
Antonio Di Monaco, MD
Cardiology Department, Regional General Hospital "F. Miulli"
Acquaviva delle Fonti, Bari, Italy
E-mail: a.dimonaco@gmail.com
Tel: +390803054111
Fax: +390803054429

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Conflict of Interest: No conflicts of interest to declare.

Key words: Cardiac Ablation; Atrial Fibrillation; Mortality, Epidemiology, Cardiovascular disease.

Abstract

Objectives. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with substantial morbidity and mortality. Data on long-term risk after catheter ablation of AF are lacking and the mortality compared with the general population is not well characterized.

Setting: We analysed data from patients residents in Apulia region underwent to AF ablation between January 2009 and June 2019.

Participants: 1260 patients (914 males, mean age 60±11 years).

Outcome: Vital status and dates of death to December 31, 2019, were obtained by using regional Health Information System. The expected number of deaths was derived using mortality rates from the general regional population by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population.

Results. During follow-up (6449 person-year), 95 deaths were observed (1.47 deaths per 100 person-year). Although overall long-term mortality after AF ablation was not different to that of the general population (SMR 1.05; 95%CI 0.86-1.28; p=0.658), the number of observed events was significantly increased in patients with heart failure (HF) at baseline or developing it during follow-up (SMR 2.40; 95%CI 1.69-3.41 and 1.75; 95%CI 1.17-2.64; respectively p<0.001 and p=0.007) and lower in those without (SMR 0.63; 95%CI 0.47-0.86 p=0.003).

Conclusion. Long-term mortality of patients undergoing AF ablation is similar to that of general population. Patients with HF had an increased risk than overall expected while those without seem to have a better risk profile.

Strengths and limitations of this study

- Long-term mortality evaluation among patients underwent to catheter ablation of atrial fibrillation.
- Standardized Mortality Ratios after procedure estimated in comparison to general population expected values.
- Mortality in patients with and without heart failure.
- Observational registry from single Italian center with a high procedural volume.
- Analysis of mortality compared to regional and national age- and gender-specific rate.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population [1]. AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health, and health economy. Subjects with AF are more likely than subjects without AF to have cardiovascular disease risk factors and preexisting disease, including heart failure [2-4].

Mid-term risk of death in AF patients varies according to the clinical setting: from 16.4 deaths per 100 person-year of patients hospitalized in a cardiology ward [5] to a rate of 3.7 fatal events per 100 person-year in AF patients enrolled in anticoagulation trials having mortality among outcomes [6]. In real-world patients with AF, the incidence of death is estimated to be, respectively, 1.0 and 3.6 per 100 person-year in those ablated and non-ablated who receive medical therapy (antiarrhythmic drugs or rate control drugs) [7]. Compared to subjects without AF, in a longitudinal population-based cohort, AF has been detected as a multivariate predictor of death that remained associated with mortality also in subjects initially free of clinically relevant cardiovascular disease [4]. Among death predictors, HF is included in prognostic scores to evaluate mortality risk of AF patients [5,6]. Catheter ablation has become an important treatment modality for patients with symptomatic drug-refractory paroxysmal and non-paroxysmal AF [8]. Furthermore, several randomized clinical trials have reported that both AF and HF outcomes can be improved with catheter ablation [9-12]. In a meta-analysis of randomized clinical trials evaluating patients with AF and coexisting left ventricular systolic dysfunction, catheter ablation has been associated with significant improvements in the clinical, structural, and functional capacity compared with AF medical treatment [13]. Compared to medical therapy, patients ablated for AF have reduced risk of heart failure and stroke as well as the death-rate [7].

Although data on long-term risks after catheter ablation of AF with or without HF has been identified [1, 7-13], those compared with the general population are not well characterized.

The purpose of this study was to evaluate all-cause mortality and to perform a population-based assessment of the long-term risk of death in patients who underwent to catheter ablation of AF compared to the whole general population.

Methods

Data were derived from the Cardiac Interventional Registry implemented at our hospital (all the interventional procedures carried out at our Center have been recorded in this Registry since 2009). Atrial fibrillation was defined according to the European Society of Cardiology guidelines [1]. We selected AF ablation procedures performed between January 2009 and June 2019. In particular, all patients had an electrocardiographic documentation of AF and the arrhythmia was symptomatic and unresponsive to at least one antiarrhythmic drug [1]. Moreover, HF was defined according to the European Society of Cardiology guidelines [4] and we included in this analysis all clinical condition that required hospitalization. All patients provided written informed consent. The study complied with the principles of the Declaration of Helsinki. Vital status and dates of death to December 31, 2019, were obtained for residents in Apulia by using regional Health Information System. Follow-up was considered to be administratively censored on December 31, 2019, and was at least 6 months for all patients (maximum, 11 years). Person-years were computed from the date of procedure to death or end of the follow-up. The expected numbers of deaths were derived using mortality rates from the general population of Apulia Region and Italian general population by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics (https://www.istat.it/).

Statistical analysis. Data were reported as mean ± standard deviation, median with interquartile range or number with percentage. Patients' characteristics at the time of procedure of AF ablation were compared according to the presence and occurrence of HF by using the Analysis of Variance, Chi-squared or Fisher Exact test as appropriate. Cox proportional-hazards model was used to estimate Hazard Ratios (HRs) with 95% confidence intervals (CI). Kaplan-Meier curves were used to describe mortality over time and the Log-Rank test to compare survival by age groups or presence of HF history. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population. The 95% CI of SMRs were estimated using the Poisson distribution considering the expected risk of death as exposure variable. A p value of 0.05 or less was considered statistically significant. All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, Tex).

Patient and Public Involvement: No patient involved.

Results

During study period, a total of 1260 patients resident in Apulia Region underwent AF catheter ablation. More than two-thirds were males with a mean age of 60±11 years. Patients younger than 55 years were 368 (29.2%) while 453 (36.0%) were in the range 55-65 and 439 (34.8%) were older than 65. At baseline, 141 (11.2%) patients had history of HF.

Over a total of 6449 person-year follow-up (mean 5.1±3.0 years; median 4.8 and interquartile range 2.6-7.6 years), HF was diagnosed in 87 patients without history of HF at the time of AF ablation procedure and an overall number of 95 deaths were observed. Table 1 shows baseline patients' characteristics at the time of procedure of AF ablation by HF (1032 without HF at baseline and during the follow-up, 141 with history of HF at baseline and 87 with new onset of HF during follow-up). Compared to patients without HF, those with history of it at baseline or those developing HF during follow-up were older with a higher prevalence of hypertension, diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, vascular and coronary artery disease, cardiac surgery.

Figure 1 (panel A, B and C) shows Kaplan-Meier curves of cumulative mortality over time after catheter ablation of AF in the overall cohort, by age group and in those with or without HF at baseline. Greater age and history of HF were significantly associated to mortality risk (Figure 1, panel B and C). History of HF had a crude HR of 4.60 (95%CI 3.00-7.08; p<0.001) with an age- and sex-adjusted value of 3.06 (1.97-4.76; p<0.001).

Table 2 shows follow-up data and reports mortality in comparison to expected risk in the general population and Figure 2 displays graphically the estimated SMR with 95%CI of observed than expected in regional population. In the overall cohort, the 10-year mortality rate was 14.2% without a significant excess of mortality than expect in the general population of the same age and gender (SMR 1.05; 95%CI 0.86-1.28; p=0.658). Although the 10-year mortality rate increased across age groups (1.7% in <55, 7.3% in 55-65 and 32.3% in those >65years), the comparison with the expected risk was not statistically significant: SMR 0.96 (95%CI 0.40-2.31 p=0.929), 1.02 (95%CI 0.65-1.60 p=0.933) and 1.06 (95%CI 0.84-1.34 p=0.620), respectively for patients in the group of <55, 55-65 and >65years. Patients with HF at baseline or those a new onset during follow-up had a high mortality rate (respectively 41.5% and 35.1%) than those without (Table 2). Compared to general population risk, an excess of mortality was observed in patients with HF at baseline (SMR 2.40; 95%CI 1.69-3.41 p=0.001) and in those with a new onset during follow-up (SMR 1.75; 95%CI 1.17-2.64 p=0.007). In patients without HF, a lower risk than expected was observed especially among those remaining free from HF during follow-up (Table 2). The SMR of 0.82 (95%CI 0.64-1.05; p=0.117) in patients without history of HF at baseline, was significant in those free from HF during follow-up (0.63; 95%CI 0.47-0.86 p=0.003).

When observed mortality was compared to Italian general population, all results were similar to the results in Apulia (Table 2).

Discussion

In the current study, we provide a long-term analysis of mortality among patients with symptomatic AF underwent to catheter ablation with respect to age and HF coexistence as well as we assessed the risk of death compared with that in the general regional population over the same period.

Beyond the association of the absolute risk with patients' age and presence of HF, the main finding of this study was that the overall long-term mortality of patients ablated for AF was not different than general population. Second, mortality after AF ablation was higher in subjects with a pre-existing history of HF and in those with a diagnosis made during follow-up. In AF patients without HF, observed deaths were lower than expected according to regional mortality rates. The analyses of long-term outcome were based on a cohort from an Italian center with a high procedural volume and on expected risk over a follow-up up to 11 years considering age- and gender-specific annual mortality rates of the general regional population.

Mortality in patients undergoing ablation of AF appears to be associated with a reduced mortality compared to drug therapy [1,8]. No previous studies reported mortality data in patients undergoing AF ablation compared to the general population. Our analysis showed that the long-term mortality after AF ablation was not higher than the risk of subjects from general population of the same patients' age and gender suggesting that after catheter ablation the clinical outcome of patients may be good enough to observe a number of deaths not different than the one expected in general population. However, a mortality gap between patients with and without HF was observed. The coexistence of AF with HF was associated with an excess mortality after the ablation procedure while patients without HF had a mortality rate better than general population.

Although AF leads to increased death rates, a better management of this condition may have reduced the net impact of AF on mortality over time [14-15]. The growing availability and use of catheter ablation of AF may partially explain the mortality reduction. Most of patients are treated with medical therapy that, compared to the ablated one, are older with more frequent comorbidities and at higher risk of death, heart failure admission, and stroke [7]. Evidence of beneficial impact of AF ablation on death is lacking. The CABANA trial did not show superiority of ablation versus drug therapy for a combined primary outcome including death, stroke, severe bleeding or cardiac arrest [16] while the CASTLE-AF trial reported lower mortality associated with ablation in patients with AF and heart failure with reduced ejection fraction [10]. Recent data including HF patients with preserved ejection fraction and AF, compared to medical therapy, catheter ablation decreases HF hospitalization and symptoms [17-19].

Compared to randomized trials, often based on combined end-points to increase statistical power, and epidemiologic evaluations of mortality after catheter ablation of AF, this study was focused on a long-term evaluation of death rate compared to general population over the same period. Findings of our study provide important insight regarding health risks after catheter ablation compared to general population useful in counselling of patients symptomatic for AF.

Although previous data reported that ablation improves outcome in patients with AF e HF [9-12], our analysis reported that mortality of patients with HF who underwent AF catheter ablation persists higher compared to general population. The mortality data were similar in patients with HF documented at admission compared to patients who had the onset of HF during follow up. These data suggest that an early treatment of AF to avoid persistent forms and an optimal HF treatment are crucial to improve outcome in these patients. The increased mortality found in our cohort of HF patients may be explained by the differences in survival of AF patients with and without HF. The incidence rate after new AF is higher in HF patients with reduced than preserved ejection fraction (30.2 vs 25.7 deaths per 100 person-year) while those without HF are at much more lower risk (12 deaths per 100 person-year) [20]. Moreover, in patients with HF, the association of AF with worse cardiovascular outcomes is significant in patients with reduced and mid-range ejection fraction but not in those with preserved systolic function [21]. Data from Framingham Heart Study show that AF occurs in more than half of individuals with HF and that HF occurs in more than one third of individuals with AF [20]. The onset of AF precedes and follows both HF (both preserved and reduced ejection fraction). However, AF and HF conjointly lead to a poor prognosis, with a higher risk among those with reduced ejection fraction [20]. In absence of HF, according to our data, mortality after cardiac ablation of AF was lower than general population. A significant risk for mortality has been reported for AF at older age (70 years or more) in adjusted analyses based on a large cohort of adult and elderly European men and women [22]. At younger age, from 40 to 69 years, the risk of mortality over a follow-up time of up 10 years was not significantly related to new-onset AF [22]. Patients with HF were older than those without. In general population, other morbidities than cardiovascular diseases affect overall survival. Neoplasms and are the first leading cause of years of life lost and deaths [23]. It is possible that patients underwent to catheter ablation of AF without history of HF and remaining free from it after the procedure are at lower risk than unselected general population also because the risk of AF diagnosis is influenced by socioeconomic factors and patients demographic differences exist in the use of catheter ablation [24-25].

The present study has several limitations. Data are from a single institution that is a reference center for percutaneous ablation of arrhythmias. We compared all causes of death mortality in the study cohort to the general population and we performed subgroup analyses only according to HF presence at baseline or by its occurrence during follow-up. For a complete analysis of the effect of comorbidities on different causes of death, comorbidity information for both patients and reference population are necessary. On the other hand, the main purpose of the present epidemiologic study was to analyze overall long term mortality in patients, selecting those at lower risk, and compare it to general population without identifying prognostic factors.

Conclusions

Long-term mortality of patients undergoing AF ablation is similar to that of the general population suggesting that after this therapeutic procedure there is no excess of mortality than overall expected. Compared to general population risk, patients with HF have a significantly higher probability of death while those without HF seem to have a better risk profile.

Data availability statement

Data are available upon reasonable request.

Ethics statements

Patient consent for publication

Not required.

Ethics approval

Ethical approval number 5690 of the Azienda Universitaria Ospedaliera Consorziale - Policlinico Bari of Bari.

Footnotes

Antonio Di Monaco contributed to the study conception and design, wrote the manuscript and have approved the final version,

Nicola Vitulano contributed to the study conception and design, provided critical feedback on subsequent drafts of the manuscript and have approved the final version

Federica Troisi provided critical feedback on subsequent drafts of the manuscript and have approved the final version

Federico Quadrini provided critical feedback on subsequent drafts of the manuscript and have approved the final version

Pietro Guida contributed to the statistical analysis and have approved the final version

Massimo Grimaldi provided critical feedback on subsequent drafts of the manuscript and have approved the final version.

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Competing interests None declared.

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Figure legends

Figure 1. Kaplan-Meier mortality estimate curve in overall patients (panel A), in those stratified by age at the time of catheter ablation of atrial fibrillation (panel B), and by the presence of heart failure (panel C).

Figure 2. Standardized mortality ratios with 95% confidence interval relative to the comparison between observed mortality and the expected from general population of Apulia Region.

Table 1. Patients' characteristics at the time of procedure of atrial fibrillation ablation and the number of deaths according to the presence and occurrence of heart failure.

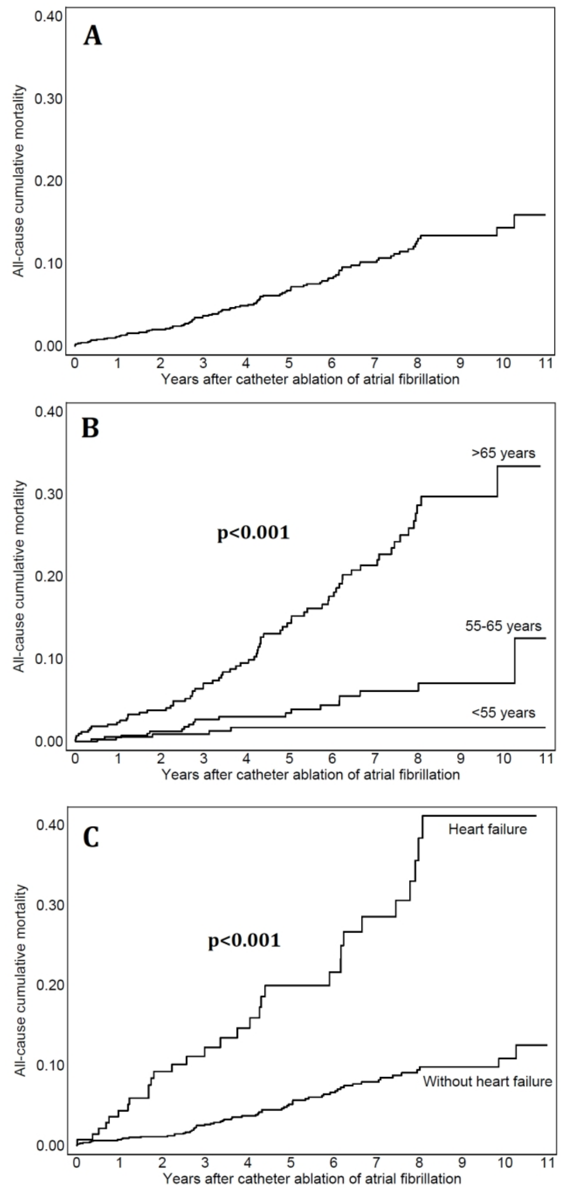
	Overall n=1260	**Without heart failure[1]** n=1032	**History of heart failure at baseline** n=141	**New onset of heart failure during follow-up** n=87	**P for difference[2]**
Males	914 (72.5%)	751 (72.8%)	110 (78.0%)	53 (60.9%)	0.018
Age (years)	60±11	59±11	64±11	66±12	<0.001
Hypertension	615 (48.8%)	469 (45.4%)	85 (60.3%)	61 (70.1%)	0.001
Diabetes mellitus	115 (9.1%)	64 (6.2%)	27 (19.1%)	24 (27.6%)	<0.001
Chronic renal disease	48 (3.8%)	26 (2.5%)	17 (12.1%)	5 (5.7%)	0.004
COPD	86 (6.8%)	47 (4.6%)	30 (21.3%)	9 (10.3%)	<0.001
Vascular disease	61 (4.8%)	41 (4.0%)	16 (11.3%)	4 (4.6%)	0.002
Coronary artery disease	86 (6.8%)	54 (5.2%)	21 (14.9%)	11 (12.6%)	0.009
Cardiac surgery	30 (2.4%)	17 (1.6%)	6 (4.3%)	7 (8.0%)	0.001
Previous stroke or TIA	32 (2.5%)	27 (2.6%)	3 (2.1%)	2 (2.3%)	1.000
History of cancer	68 (5.4%)	52 (5.0%)	10 (7.1%)	6 (6.9%)	0.418
Deaths during the follow-up	95	41	31	23	

[1]No heart failure at baseline and during the follow-up.
[2]P for difference was calculated by Analysis of Variance, Chi-squared or Fisher Exact test as appropriate.
Mean ± Standard Deviation, number and percentage of patients. COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischemic Attack.

Table 2. Mortality and expected risk during follow-up with standardized mortality ratios in relation to age categories, history of heart failure and development of heart failure.

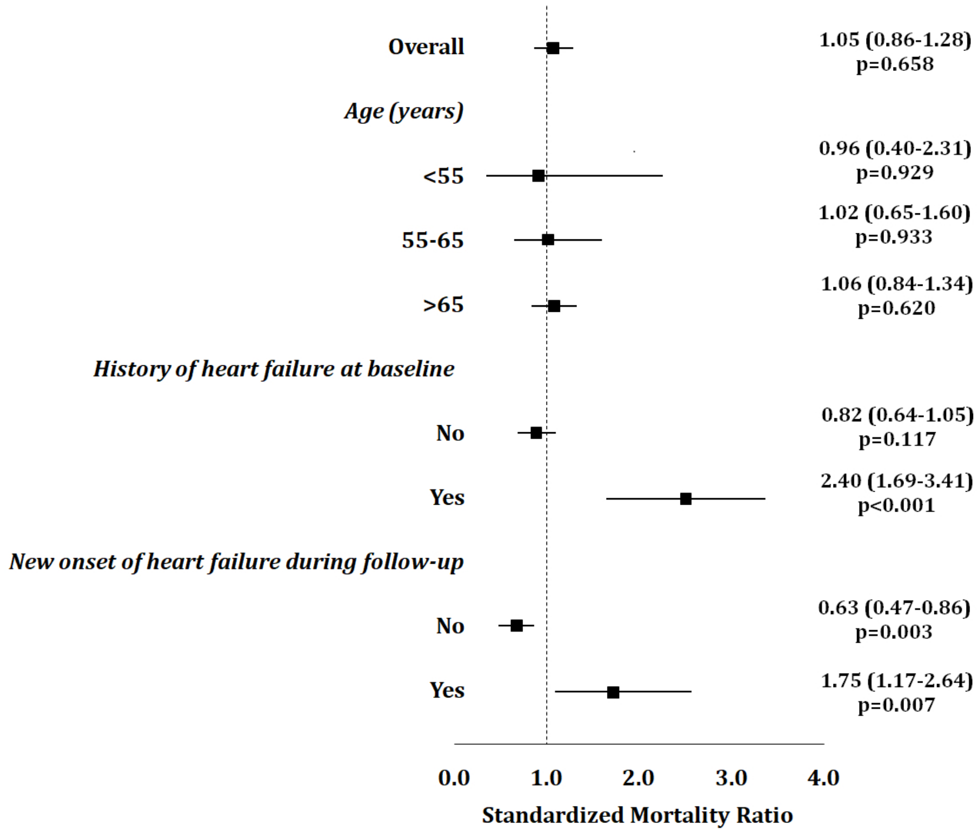
	Patients n	Deaths (n)	10-year mortality rate (%)	Follow-up (Person-Years)	Event-Rate (100 Person-Years)	Expected Deaths in Apulia (n)	SMR (95%CI) vs Apulia	Expected Deaths in Italy (n)	SMR (95%CI) vs Italy
Overall	1260	95	14.2	6449	1.47	90.8	1.05 (0.86-1.28) p=0.658	92.9	1.02 (0.84-1.25) p=0.829
Age (years)									
<55	368	5	1.7	1992	0.25	5.2	0.96 (0.40-2.31) p=0.929	5.4	0.93 (0.39-2.23) p=0.0.871
55-65	453	19	7.3	2333	0.81	18.6	1.02 (0.65-1.60) p=0.933	19.6	0.97 (0.62-1.52) p=0.888
>65	439	71	32.2	2124	3.34	66.9	1.06 (0.84-1.34) p=0.620	67.9	1.05 (0.83-1.32) p=0.708
History of heart failure at baseline									
No	1119	64	10.8	5825	1.10	77.8	0.82 (0.64-1.05) p=0.117	79.7	0.80 (0.63-1.03) p=0.079
Yes	141	31	41.5	623	4.98	12.9	2.40 (1.69-3.41) p<0.001	13.2	2.34 (1.65-3.33) p<0.001
**New onset of heart failure during follow-up*									
No	1032	41	7.0	5259	0.78	64.7	0.63 (0.47-0.86) p=0.003	66.3	0.62 (0.46-0.84) p=0.002
Yes	87	23	35.1	567	4.06	13.1	1.75 (1.17-2.64) p=0.007	13.4	1.72 (1.14-2.59) p=0.009

CI = Confidence Interval; SMR = Standardized mortality ratio. *New heart failure onset refers to 1119 patients without history of heart failure at the time of procedure of atrial fibrillation ablation. The p values were calculated according to Poisson model.



Kaplan-Meier mortality estimate curve in overall patients (panel A), in those stratified by age at the time of catheter ablation of atrial fibrillation (panel B), and by the presence of heart failure (panel C).

322x692mm (96 x 96 DPI)



Standardized mortality ratios with 95% confidence interval relative to the comparison between observed mortality and the expected from general population of Puglia Region.

304x261mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 2; rows 1-22)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (page 4, rows 1-23)
Objectives	3	State specific objectives, including any prespecified hypotheses (page 4, rows 24-24) (page 5, rows 1-4)
Methods		
Study design	4	Present key elements of study design early in the paper (page 5, rows 5-12)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 5, rows 13-18)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case (page 5, rows 5-18)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (page 5, rows 19-26) (page 6, rows 1-4)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (page 5, rows 19-26) (page 6, rows 1-4)
Bias	9	Describe any efforts to address potential sources of bias (page 5, rows 19-26) (page 6, rows 1-4) (page 10; rows 9-16)
Study size	10	Explain how the study size was arrived at (page 5, rows 19-26) (page 6, rows 1-4)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (page 5, rows 19-26) (page 6, rows 1-4)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of

sampling strategy (page 5, rows 19-26) (page 6, rows 1-4)

(e) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram (page 6, rows 8-9)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (page 6, rows 8-15)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures (page 6, rows 16-20) (page 7, rows 1-22)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (page 6, rows 16-20) (page 7, rows 1-22)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (page 6, rows 16-20) (page 7, rows 1-22)
Discussion		
Key results	18	Summarise key results with reference to study objectives (page 7, rows 25-26) (page 8, rows 1-9)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 10, rows 9-16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (page 10, rows 18-22)
Generalisability	21	Discuss the generalisability (external validity) of the study results (page 9, rows 4-11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page 11, row 21)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Long-term mortality of patients ablated for atrial fibrillation: a retrospective, population-based epidemiological study in Apulia, Italy

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Long-term mortality of patients ablated for atrial fibrillation: a retrospective, population-based epidemiological study in Apulia, Italy

Antonio Di Monaco[1,2] MD, Nicola Vitulano[1] MD, Federica Troisi[1] MD PhD, Federico Quadrini[1] MD, Pietro Guida[1], Massimo Grimaldi[1] MD PhD

1 Cardiology Department, Regional General Hospital "F. Miulli", Acquaviva delle Fonti, Bari, Italy.
2 Department of Clinical and Experimental Medicine, University of Foggia, Italy.

Corresponding author:
Antonio Di Monaco, MD
Cardiology Department, Regional General Hospital "F. Miulli"
Acquaviva delle Fonti, Bari, Italy
E-mail: a.dimonaco@gmail.com
Tel: +390803054111
Fax: +390803054429

Abstract

Objectives: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with substantial morbidity and mortality. Data on long-term risk and mortality after catheter ablation of AF are lacking. The aim of this study was to evaluate all-cause mortality and the long-term risk of death in patients who underwent to catheter ablation of AF compared to the general population

Design: Retrospective, population-based epidemiological study.

Setting: We analysed data from patients resident in Apulia region who underwent AF ablation between January 2009 and June 2019.

Participants: 1260 patients (914 male, mean age 60±11 years).

Outcomes: Vital status and dates of death to December 31, 2019, were obtained by using regional Health Information System. The expected number of deaths was derived using mortality rates from the general regional population by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population.

Results: During follow-up (6449 person-years), 95 deaths were observed (1.47 deaths per 100 person-years). Although overall long-term mortality after AF ablation was not different to that of the general population (SMR 1.05 [95% CI 0.86-1.28; p=0.658]), the number of observed events was significantly increased in patients with heart failure (HF) at baseline or who developed HF during follow-up (SMR 2.40 [1.69-3.41; p<0.001] and 1.75 [1.17-2.64; p=0.007]; respectively) and reduced in those without (SMR 0.63 [0.47-0.86; p=0.003]).

Conclusion. Long-term mortality of patients undergoing AF ablation is similar to that of general population. Patients with HF had an increased risk while those without seem to have a better risk profile.

Keywords: Cardiac ablation; atrial fibrillation; mortality; epidemiology; cardiovascular disease

Strengths and limitations of this study

- A strength of the study is that it allowed for analysis of long-term mortality among patients who underwent catheter ablation of atrial fibrillation compared to regional and national age- and gender-specific rates.
- An important limitation is that our study only involves patients from Apulia Region, which may limit its generalisability to other Italian regions or foreign countries.
- Another limitation is that data are from a single institution that is a reference center for percutaneous ablation of arrhythmias; the applicability of results to other institutions or populations of patients with different risk profile may be limited.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population [1]. AF is associated with substantial morbidity and mortality, thus portending significant burden to patients, societal health, and health economy. Subjects with AF are more likely than subjects without AF to have cardiovascular disease risk factors and preexisting disease, including heart failure [2-4].

Mid-term risk of death in AF patients varies according to the clinical setting: from 16.4 deaths per 100 person-year of patients hospitalized in a cardiology ward [5] to a rate of 3.7 fatal events per 100 person-year in AF patients enrolled in anticoagulation trials having mortality among outcomes [6]. In real-world patients with AF, the incidence of death is estimated to be, respectively, 1.0 and 3.6 per 100 person-year in those ablated and non-ablated who receive medical therapy (antiarrhythmic drugs or rate control drugs) [7]. Compared to subjects without AF, in a longitudinal population-based cohort, AF has been detected as a multivariate predictor of death that remained associated with mortality also in subjects initially free of clinically relevant cardiovascular disease [4]. Among death predictors, HF is included in prognostic scores to evaluate mortality risk of AF patients [5,6].

Catheter ablation has become an important treatment modality for patients with symptomatic drug-refractory paroxysmal and non-paroxysmal AF [8]. Furthermore, several randomized clinical trials have reported that both AF and HF outcomes can be improved with catheter ablation [9-12]. In a meta-analysis of randomized clinical trials evaluating patients with AF and coexisting left ventricular systolic dysfunction, catheter ablation has been associated with significant improvements in the clinical, structural, and functional capacity compared with AF medical treatment [13]. Compared to medical therapy, patients ablated for AF have reduced risk of heart failure and stroke as well as the death-rate [7].

Although data on long-term risks after catheter ablation of AF with or without HF has been identified [1, 7-13], those compared with the general population are not well characterized.

The purpose of this study was to evaluate all-cause mortality and to perform a population-based assessment of the long-term risk of death in patients who underwent to catheter ablation of AF compared to the whole general population.

Methods

Study design and setting

Data were retrospectively derived from the Cardiac Interventional Registry implemented at our hospital (all the interventional procedures carried out at our Center have been recorded in this Registry since 2009). Atrial fibrillation was defined according to the European Society of Cardiology guidelines [1]. We selected AF ablation procedures performed between January 2009 and June 2019. In particular, all patients had an electrocardiographic documentation of AF and the arrhythmia was symptomatic and unresponsive to at least one antiarrhythmic drug [1]. Moreover, HF was defined according to the European Society of Cardiology guidelines [4] and we included in this analysis all clinical condition that required hospitalization. All patients provided written informed consent. The study complied with the principles of the Declaration of Helsinki. Vital status and dates of death to December 31, 2019, were obtained for residents in Apulia by using regional Health Information System. Follow-up was considered to be administratively censored on December 31, 2019, and was at least 6 months for all patients (maximum, 11 years). Person-years were computed from the date of procedure to death or end of the follow-up. The expected numbers of deaths were derived using mortality rates from the general population of Apulia Region and Italian general population by considering age- and gender-specific death probability provided for each calendar year by Italian National Institute of Statistics (https://www.istat.it/).

Statistical analysis

Data were reported as mean ± standard deviation, median with interquartile range or number with percentage. Patients' characteristics at the time of procedure of AF ablation were compared according to the presence and occurrence of HF by using the Analysis of Variance, Chi-squared or

Fisher Exact test as appropriate. Cox proportional-hazards model was used to estimate Hazard Ratios (HRs) with 95% confidence intervals (CI). Kaplan-Meier curves were used to describe mortality over time and the Log-Rank test to compare survival by age groups or presence of HF history. Standardized Mortality Ratios (SMRs) were calculated by dividing the observed number of deaths among patients by the expected number of deaths estimated from the general population. The 95% CI of SMRs were estimated using the Poisson distribution considering the expected risk of death as exposure variable. A p value of 0.05 or less was considered statistically significant. All analyses were conducted using STATA software, version 16 (Stata-Corp LP, College Station, Tex).

Patient and public involvement

No patient involved.

Results

During study period, a total of 1260 patients resident in Apulia Region underwent AF catheter ablation. More than two-thirds were males with a mean age of 60±11 years. Patients younger than 55 years were 368 (29.2%) while 453 (36.0%) were in the range 55-65 and 439 (34.8%) were older than 65. At baseline, 141 (11.2%) patients had history of HF.

Over a total of 6449 person-year follow-up (mean 5.1±3.0 years; median 4.8 and interquartile range 2.6-7.6 years), HF was diagnosed in 87 patients without history of HF at the time of AF ablation procedure and an overall number of 95 deaths were observed. Table 1 shows baseline patients' characteristics at the time of procedure of AF ablation by HF (1032 without HF at baseline and during the follow-up, 141 with history of HF at baseline and 87 with new onset of HF during follow-up). Compared to patients without HF, those with history of it at baseline or those developing HF during follow-up were older with a higher prevalence of hypertension, diabetes mellitus, chronic renal disease, chronic obstructive pulmonary disease, vascular and coronary artery disease, cardiac surgery.

Figure 1 (panel A, B and C) shows Kaplan-Meier curves of cumulative mortality over time after catheter ablation of AF in the overall cohort, by age group and in those with or without HF at baseline. Greater age and history of HF were significantly associated to mortality risk (Figure 1, panel B and C). History of HF had a crude HR of 4.60 (95% CI 3.00-7.08; p<0.001) with an age- and sex-adjusted value of 3.06 (1.97-4.76; p<0.001).

Table 2 shows follow-up data and reports mortality in comparison to expected risk in the general population and Figure 2 displays graphically the estimated SMR with 95% CI of observed than expected in regional population. In the overall cohort, the 10-year mortality rate was 14.2% without a significant excess of mortality than expect in the general population of the same age and gender (SMR 1.05, 95% CI 0.86-1.28; p=0.658). Although the 10-year mortality rate increased across age groups (1.7% in <55, 7.3% in 55-65 and 32.3% in those >65years), the comparison with the expected risk was not statistically significant: SMR 0.96 (95% CI 0.40-2.31; p=0.929), 1.02 (95% CI 0.65-1.60; p=0.933) and 1.06 (95% CI 0.84-1.34; p=0.620), respectively, for patients in the group of <55, 55-65 and >65 years. Patients with HF at baseline or those a new onset during follow-up had a high mortality rate (respectively 41.5% and 35.1%) than those without (Table 2).

Compared to general population risk, an excess of mortality was observed in patients with HF at baseline (SMR 2.40, 95% CI 1.69-3.41 p=0.001) and in those with a new onset during follow-up (SMR 1.75, 95% CI, 1.17-2.64 p=0.007). In patients without HF, a lower risk than expected was observed especially among those remaining free from HF during follow-up (Table 2). The SMR of 0.82 (95% CI 0.64-1.05; p=0.117) in patients without history of HF at baseline, was significant in those free from HF during follow-up (0.63, 95% CI 0.47-0.86; p=0.003).

When observed mortality was compared to Italian general population, all results were similar to the results in Apulia (Table 2).

Discussion

In the current study, we provide a long-term analysis of mortality among patients with symptomatic AF underwent to catheter ablation with respect to age and HF coexistence as well as we assessed the risk of death compared with that in the general regional population over the same period. Beyond the association of the absolute risk with patients' age and presence of HF, the main finding of this study was that the overall long-term mortality of patients ablated for AF was not different than general population. Second, mortality after AF ablation was higher in subjects with a pre-existing history of HF and in those with a diagnosis made during follow-up. In AF patients without HF, observed deaths were lower than expected according to regional mortality rates. The analyses of long-term outcome were based on a cohort from an Italian center with a high procedural volume and on expected risk over a follow-up up to 11 years considering age- and gender-specific annual mortality rates of the general regional population.

Mortality in patients undergoing ablation of AF appears to be associated with a reduced mortality compared to drug therapy [1,8]. No previous studies reported mortality data in patients undergoing AF ablation compared to the general population. Our analysis showed that the long-term mortality after AF ablation was not higher than the risk of subjects from general population of the same patients' age and gender suggesting that after catheter ablation the clinical outcome of patients may be good enough to observe a number of deaths not different than the one expected in general population. However, a mortality gap between patients with and without HF was observed. The coexistence of AF with HF was associated with an excess mortality after the ablation procedure while patients without HF had a mortality rate better than general population.

Although AF leads to increased death rates, a better management of this condition may have reduced the net impact of AF on mortality over time [14-15]. The growing availability and use of catheter ablation of AF may partially explain the mortality reduction. Most of patients are treated with medical therapy that, compared to the ablated one, are older with more frequent comorbidities and at higher risk of death, heart failure admission, and stroke [7]. Evidence of beneficial impact of AF ablation on death is lacking. The CABANA trial did not show superiority of ablation versus drug therapy for a combined primary outcome including death, stroke, severe bleeding or cardiac arrest [16] while the CASTLE-AF trial reported lower mortality associated with ablation in patients with AF and heart failure with reduced ejection fraction [10]. Recent data including HF patients with preserved ejection fraction and AF, compared to medical therapy, catheter ablation decreases HF hospitalization and symptoms [17-19].

Compared to randomized trials, often based on combined end-points to increase statistical power, and epidemiologic evaluations of mortality after catheter ablation of AF, this study was focused on a long-term evaluation of death rate compared to general population over the same period. Findings of our study provide important insight regarding health risks after catheter ablation compared to general population useful in counselling of patients symptomatic for AF.

Although previous data reported that ablation improves outcome in patients with AF e HF [9-12], our analysis reported that mortality of patients with HF who underwent AF catheter ablation persists higher compared to general population. The mortality data were similar in patients with HF documented at admission compared to patients who had the onset of HF during follow up. These data suggest that an early treatment of AF to avoid persistent forms and an optimal HF treatment are crucial to improve outcome in these patients. The increased mortality found in our cohort of HF patients may be explained by the differences in survival of AF patients with and without HF. The incidence rate after new AF is higher in HF patients with reduced than preserved ejection fraction (30.2 vs 25.7 deaths per 100 person-year) while those without HF are at much more lower risk (12 deaths per 100 person-year) [20]. Moreover, in patients with HF, the association of AF with worse cardiovascular outcomes is significant in patients with reduced and mid-range ejection fraction but not in those with preserved systolic function [21]. Data from Framingham Heart Study show that AF occurs in more than half of individuals with HF and that HF occurs in more than one third of individuals with AF [20]. The onset of AF precedes and follows both HF (both preserved and reduced ejection fraction). However, AF and HF conjointly lead to a poor prognosis, with a higher risk among those with reduced ejection fraction [20]. In absence of HF, according to our data, mortality after cardiac ablation of AF was lower than general population. A significant risk for mortality has been reported for AF at older age (70 years or more) in adjusted analyses based on a large cohort of adult and elderly European men and women [22]. At younger age, from 40 to 69 years, the risk of mortality over a follow-up time of up 10 years was not significantly related to new-onset AF [22]. Patients with HF were older than those without. In general population, other morbidities than cardiovascular diseases affect overall survival. Neoplasms and are the first leading cause of years of life lost and deaths [23]. It is possible that patients underwent to catheter ablation of AF without history of HF and remaining free from it after the procedure are at lower risk than unselected general population also because the risk of AF diagnosis is influenced by socioeconomic factors and patients demographic differences exist in the use of catheter ablation [24-25].

The present study has several limitations. Data are from a single institution that is a reference center for percutaneous ablation of arrhythmias. We compared all causes of death mortality in the study cohort to the general population and we performed subgroup analyses only according to HF presence at baseline or by its occurrence during follow-up. For a complete analysis of the effect of comorbidities on different causes of death, comorbidity information for both patients and reference population are necessary. On the other hand, the main purpose of the present epidemiologic study was to analyze overall long-term mortality in patients, selecting those at lower risk, and compare it to general population without identifying prognostic factors.

Conclusions

Long-term mortality of patients undergoing AF ablation is similar to that of the general population suggesting that after this therapeutic procedure there is no excess of mortality than overall expected. Compared to general population risk, patients with HF have a significantly higher probability of death while those without HF seem to have a better risk profile.

Contributors

Antonio Di Monaco contributed to the study conception and design, wrote the manuscript and approved the final version; Nicola Vitulano contributed to the study conception and design, provided critical feedback on drafts of the manuscript and approved the final version; Federica Troisi provided critical feedback on drafts of the manuscript and approved the final version; Federico Quadrini provided critical feedback on drafts of the manuscript and approved the final version; Pietro Guida contributed to the statistical analysis and approved the final version of the manuscript; Massimo Grimaldi provided critical feedback on drafts of the manuscript and approved the final version.

Funding

None.

Competing interests

None declared.

Data availability statement

Data are available upon reasonable request.

Patient consent for publication

Not required.

Ethics approval

Ethical approval number 5690 of the Azienda Universitaria Ospedaliera Consorziale - Policlinico Bari of Bari.

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Figure titles

Figure 1. Kaplan-Meier mortality estimate curve in overall patients (panel A), in those stratified by age at the time of catheter ablation of atrial fibrillation (panel B), and by the presence of heart failure (panel C)

Figure 2. Standardized mortality ratios with 95% confidence intervals relative to the comparison between observed mortality and the expected from general population of Apulia Region

Table 1. Patients' characteristics at the time of procedure of atrial fibrillation ablation and the number of deaths according to the presence and occurrence of heart failure

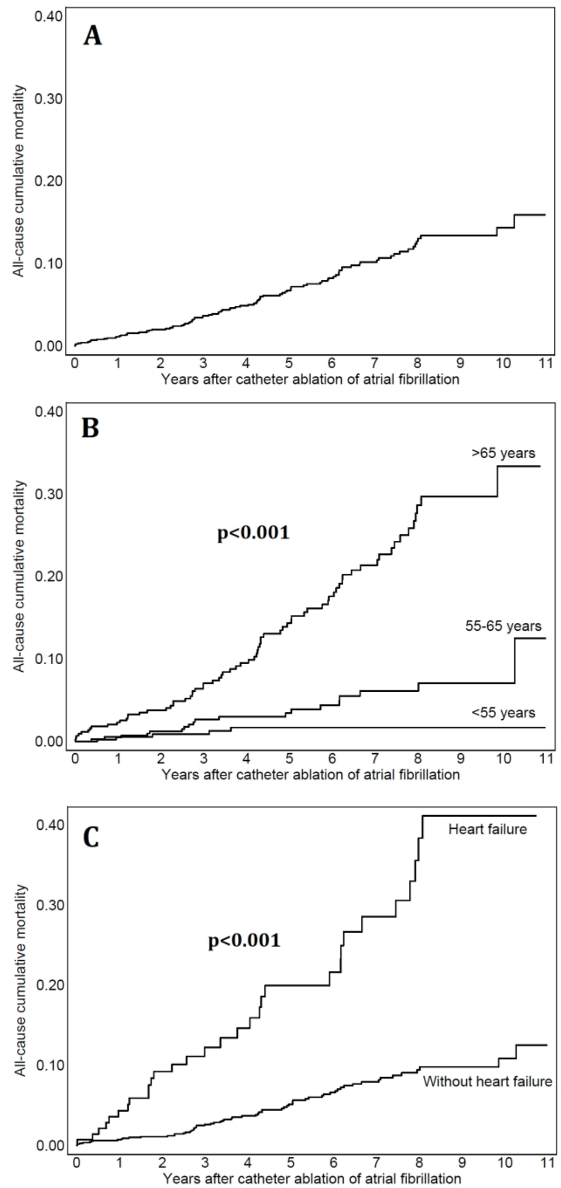
	Overall n=1260	Without heart failure[1] n=1032	History of heart failure at baseline n=141	New onset of heart failure during follow-up n=87	P for difference[2]
Males	914 (72.5%)	751 (72.8%)	110 (78.0%)	53 (60.9%)	0.018
Age (years)	60±11	59±11	64±11	66±12	<0.001
Hypertension	615 (48.8%)	469 (45.4%)	85 (60.3%)	61 (70.1%)	0.001
Diabetes mellitus	115 (9.1%)	64 (6.2%)	27 (19.1%)	24 (27.6%)	<0.001
Chronic renal disease	48 (3.8%)	26 (2.5%)	17 (12.1%)	5 (5.7%)	0.004
COPD	86 (6.8%)	47 (4.6%)	30 (21.3%)	9 (10.3%)	<0.001
Vascular disease	61 (4.8%)	41 (4.0%)	16 (11.3%)	4 (4.6%)	0.002
Coronary artery disease	86 (6.8%)	54 (5.2%)	21 (14.9%)	11 (12.6%)	0.009
Cardiac surgery	30 (2.4%)	17 (1.6%)	6 (4.3%)	7 (8.0%)	0.001
Previous stroke or TIA	32 (2.5%)	27 (2.6%)	3 (2.1%)	2 (2.3%)	1.000
History of cancer	68 (5.4%)	52 (5.0%)	10 (7.1%)	6 (6.9%)	0.418
Deaths during the follow-up	95	41	31	23	

[1]No heart failure at baseline and during the follow-up.
[2]P for difference was calculated by Analysis of Variance, Chi-squared or Fisher Exact test as appropriate.
Mean ± Standard Deviation, number and percentage of patients. COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischemic Attack.

Table 2. Mortality and expected risk during follow-up with standardized mortality ratios in relation to age categories, history of heart failure and development of heart failure

	Patients n	Deaths (n)	10-year mortality rate (%)	Follow-up (Person-Years)	Event-Rate (100 Person-Years)	Expected Deaths in Apulia (n)	SMR (95%CI) vs Apulia	Expected Deaths in Italy (n)	SMR (95%CI) vs Italy
Overall	1260	95	14.2	6449	1.47	90.8	1.05 (0.86-1.28) p=0.658	92.9	1.02 (0.84-1.25) p=0.829
Age (years)									
<55	368	5	1.7	1992	0.25	5.2	0.96 (0.40-2.31) p=0.929	5.4	0.93 (0.39-2.23) p=0.0.871
55-65	453	19	7.3	2333	0.81	18.6	1.02 (0.65-1.60) p=0.933	19.6	0.97 (0.62-1.52) p=0.888
>65	439	71	32.2	2124	3.34	66.9	1.06 (0.84-1.34) p=0.620	67.9	1.05 (0.83-1.32) p=0.708
History of heart failure at baseline									
No	1119	64	10.8	5825	1.10	77.8	0.82 (0.64-1.05) p=0.117	79.7	0.80 (0.63-1.03) p=0.079
Yes	141	31	41.5	623	4.98	12.9	2.40 (1.69-3.41) p<0.001	13.2	2.34 (1.65-3.33) p<0.001
**New onset of heart failure during follow-up*									
No	1032	41	7.0	5259	0.78	64.7	0.63 (0.47-0.86) p=0.003	66.3	0.62 (0.46-0.84) p=0.002
Yes	87	23	35.1	567	4.06	13.1	1.75 (1.17-2.64) p=0.007	13.4	1.72 (1.14-2.59) p=0.009

CI = Confidence Interval; SMR = Standardized mortality ratio. *New heart failure onset refers to 1119 patients without history of heart failure at the time of procedure of atrial fibrillation ablation. The p values were calculated according to Poisson model.



Kaplan-Meier mortality estimate curve in overall patients (panel A), in those stratified by age at the time of catheter ablation of atrial fibrillation (panel B), and by the presence of heart failure (panel C).

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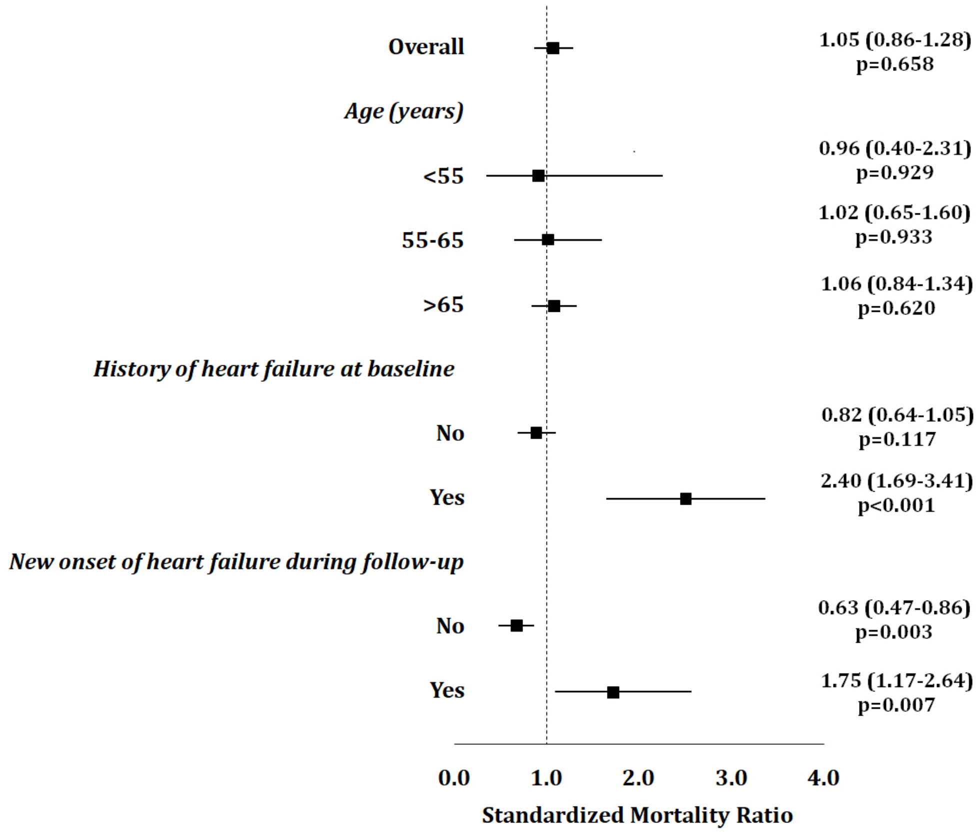

Standardized mortality ratios with 95% confidence interval relative to the comparison between observed mortality and the expected from general population of Puglia Region.

304x261mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (page 1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 2; rows 1-22)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (page 4, rows 1-23)
Objectives	3	State specific objectives, including any prespecified hypotheses (page 4, rows 24-24) (page 5, rows 1-4)
Methods		
Study design	4	Present key elements of study design early in the paper (page 5, rows 5-12)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 5, rows 13-18)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case (page 5, rows 5-18)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (page 5, rows 19-26) (page 6, rows 1-4)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (page 5, rows 19-26) (page 6, rows 1-4)
Bias	9	Describe any efforts to address potential sources of bias (page 5, rows 19-26) (page 6, rows 1-4) (page 10; rows 9-16)
Study size	10	Explain how the study size was arrived at (page 5, rows 19-26) (page 6, rows 1-4)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (page 5, rows 19-26) (page 6, rows 1-4)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of

sampling strategy (page 5, rows 19-26) (page 6, rows 1-4)

(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram (page 6, rows 8-9)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (page 6, rows 8-15)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures (page 6, rows 16-20) (page 7, rows 1-22)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (page 6, rows 16-20) (page 7, rows 1-22)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (page 6, rows 16-20) (page 7, rows 1-22)
Discussion		
Key results	18	Summarise key results with reference to study objectives (page 7, rows 25-26) (page 8, rows 1-9)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 10, rows 9-16)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (page 10, rows 18-22)
Generalisability	21	Discuss the generalisability (external validity) of the study results (page 9, rows 4-11)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page 11, row 21)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.